Chemical and Physical Basis of Pharmacological Action

A JOINT discussion in which pharmacologists and chemists took part was organized by the Royal Society at Burlington House on November 12.

Prof. A. J. Clark opened the discussion with a general review of the difficulty of obtaining quantitative pharmacological data and of interpreting these data when obtained. The observations are subject to large errors, and the results are affected by so many factors that it is usually possible to explain them in several different ways. It is never possible to obtain formal proof of any one explanation, but in many cases the analogy between the action of drugs on living organisms and their actions under simpler conditions is close enough to establish a strong presumption as to the mechanisms involved. The most hopeful line of approach lies in the study of the form of the curve connecting the concentration of a drug with the magnitude of its effect after dynamic equilibrium is obtained. Such concentration-action curves can be divided into three distinct classes :

(1) It has been shown, in many cases, that the relation between the concentration of adrenaline, or acetylcholine, and its action on an isolated piece of muscle is accurately expressed by a hyperbola. This relationship can be interpreted in terms of mass action. If the drug, present in large excess, combines reversibly with a limited number of receptors in the muscle, simple calculations suggest that the curve connecting concentration and uptake would be a hyperbola. It is only necessary to assume that the effect on the muscle is directly proportional to the number of receptors acted on by the drug. Similar calculations have been used to explain quantitatively the uptake of gases by adsorbents, of oxygen by hæmoglobin, and of poisons by enzymes.

(2) Concentration-action curves for narcotics are usually nearly linear for small concentrations, and resemble closely the curves connecting the concentration of these substances with their effect on surface tension. Since the active narcotics are those which have most effect on surface tension, it is probable that this relationship is not fortuitous. Similar curves are obtained for the action of certain drugs on enzymes.

(3) In certain cases the concentration-action curve for effects, both on living tissues and on enzymes, is *S*-shaped. This can be interpreted as an irreversible all-or-none action on a collection of cells or other elements, the accessibility, or sensitivity, of which varies.

These three types of curve are found not only in the study of the action of drugs on isolated tissues and on enzymes, but also among the 'characteristic curves' which show the relationship between the dose of a drug and the percentage mortality which it causes in a large group of animals.

These curves were also discussed by Prof. J. H. Gaddum. It is true that, when characteristic curves are plotted on an arithmetic scale of doses, the curves may be either symmetrical or asymmetrical. When they are plotted on a logarithmic scale of doses, they are always approximately symmetrical. This fact is an example of the general law, which is justified both by theory and in practice, that the logarithm of any biological measurement is more likely to be normally distributed than the measurement itself (Galton, 1879). These facts are exemplified by the work of Hemmingsen (*Vidensk. Medd. fra Dansk naturh. Foren.*, **98**, 125 ; 1934) who showed that the logarithms of the measurements of different species of animal in one phylogenetic group are normally distributed. Curves were shown in which the effect of drugs on isolated tissues, and on enzymes, and the effect of oxygen on hæmoglobin, were plotted both on arithmetic, and on logarithmic, scales of concentration. Plotted in these ways, all these curves looked similar to the characteristic curves, and it was suggested that the shape of the curves might be explained in terms of variations among the cells in the isolated tissue, or the protein molecules in the enzyme or the hæmoglobin.

Prof. W. Straub, of Munich, said that it is premature to speculate on the mechanisms behind the action of drugs until more is known of the actual effects produced. The central problem lies in the fact that atropine will act only on cells of a certain kind, and has no apparent action on all the other cells in the body. Some of the facts are illustrated by the inhibitory action of muscarine on the frog's heart. The action takes only a fraction of a second to develop, and when the solution is changed the heart recovers in a few seconds. If the muscarine is left in contact with the heart it diffuses into the heart. When diffusion ceases, the heart recovers from the inhibition. At this stage, the heart contains large quantities of muscarine. Inhibition only occurs while there is a potential gradient, or concentration gradient of muscarine, and the drug is diffusing into the heart. Drugs which act like this are called *potentialgifte*. Acetylcholine and adrenaline act as *potentialgifte*, but these two drugs, being natural constituents of the body, are destroyed in the cells, so that they can go on diffusing for long periods without the gradient disappearing. This is the reason why these substances can cause prolonged effects if the external concentration is maintained.

According to Prof. R. A. Peters, the time has come to replace the old biochemical concept of the cell as an unorganized colloidal solution by one of the cells as a co-ordinated structure. In 1929 he postulated what J. Needham has since called a cyto-skeleton for cells : by this he means a three-dimensional mosaic throughout the cell, composed of a network of protein molecules, the surface proteins being connected with the nuclear proteins by threads of cytoplasmic proteins. The amino and carboxyl groups of protein must play an important part in this pattern. The organization envisaged is submicroscopic ; it provides the cell with means for independent and localized reactions, and is the cellular counterpart of a nervous system. Since these ideas were put forward, a clearer picture of the sort of organization which might exist has been obtained by the work on the X-ray structure of proteins, on surface films and by such protein models as those suggested by Drs. D. Wrinch and Jordan Lloyd. The cell contents appear to correspond more closely to a thixotropic gel than to a simple solution. Some enzymic systems appear to be structurally related, for example, the lactate and pyruvate system in

brain. The cellular organization proposed might allow drug action to be explained in chemical terms, drugs reacting with specialized features of the cell structure.

Dr. J. F. Danielli discussed the structure of cell surfaces. The simplest possible concept of the cell plasma-membrane which is compatible with permeability data, surface tension data, and wetting properties, consists of a lipoid layer at least two molecules thick, with an adsorbed protein layer at each oil-water interface. The external oil-water interface must have an excess of acidic groups. Points of interest in this conception from the aspect of drug action are: (*a*) the excess acidity of the surface, which may be modified by surface active acids or bases; this change will in turn affect the adsorbed protein layer, enzyme activity at the surface, and the permeability of the lipoid layer; (*b*) the potential gradient at the interfaces, which will be of the order of 10^7–10^9 volts/cm.; (*c*) the kinetics of penetration of such a membrane provide for high temperature coefficients for the simple process of penetration of the membrane by a drug, which may mask the temperature coefficient of drug action; (*d*) it is of interest to know whether the enzyme centres on the cell surface are arranged in an organized fashion. This can be done by using poisons of the type A'–$(R)_n$–B' where A' and B' are specific poisons for the centres of type A and B. If there is any typical distance between A and B, there will be a sudden increase in efficiency of the poison for a particular value of n.

Dr. J. H. Quastel described the experiments with isolated pieces of tissue which have led him to the conclusion that the action of narcotics on the brain is due to their action on carbohydrate metabolism. Luminal reduces the oxygen consumption of slices of brain. It is particularly effective when glucose, lactic acid, or pyruvic acid is used as a substrate. It has no action on the oxidation of glutamic acid or succinic acid. Other narcotics have a similar action, and among narcotics of one type those which are powerful narcotics are also powerful reducers of oxygen consumption. The effect is reversible. The concentrations present in the blood during narcosis would be sufficient to have an action on the oxygen consumption of slices. Slices of tissues other than brain are less sensitive to narcotics. The action of narcotics on slices of brain is antagonized by potassium, but is not affected by calcium. The temperature coefficient of the effects on isolated slices is large ($Q_{10}=6{\cdot}6$) as is also the temperature coefficient of narcosis in the whole animal.

It was pointed out by Dr. H. R. Ing that the pharmacological properties of many drugs have been shown to depend on definite functional groups or combinations of groups. The recognition of such pharmacologically active groups is exploited in chemotherapy. Some hormones and vitamins have also been shown to contain such groups. Aliphatic narcotics do not appear to contain active groups, and consequently the drug action must depend primarily on their physical properties. Drugs with active groups of quite different structure may also show similar pharmacological properties. When gross physiological changes, for example, the death of bacteria, are involved, several mechanisms may achieve the same gross effect; but it is difficult to account for drugs so unrelated chemically as muscarine and pilocarpine acting selectively at the same sites and producing similar results. Again, drugs of the same structural type may have different actions, for example, butyl trimethyl ammonium augments, but octyl trimethyl ammonium antagonizes the action of acetylcholine on the frog's auricle.

Pharmacologically active groups seem to imply a chemical mechanism for drug action. The difference in the activity of stereo-isomeric drugs also suggests chemical combination of the drug with receptor molecules in tissues. Homologous series of drugs frequently show maximum activity for one member of the series, for example, alkylcresols, alkylamines, etc. In these cases, the activity may represent the summation of two opposite effects, depending on at least two physical properties. Other factors may be involved, such as the length of chain between two active groups, but in some series, for example, choline esters, the relatively high activity of one member is difficult to account for on these simple lines.

The factors affecting the action of chemotherapeutic drugs on Protozoa were discussed by Prof. Warrington Yorke. *Trypanosoma rhodesiense* is normally resistant to organic arsenicals, but when it is passaged through mice, there is a change in its morphology, and it becomes not only more pathogenic for mice, but also more sensitive to arsenicals. Similar changes occur more slowly when it is passaged through guinea pigs. *T. gambiense*, on the other hand, is comparatively easily killed by drugs, but if infected mice are treated with ineffective doses of organic arsenicals or antimonials or with acridine dyes, the Protozoa become resistant to all drugs of these classes. They remain sensitive to arsenious acid, tartar emetic and Bayer 205. It has been found impossible to develop resistance to tartar emetic, and difficult to develop resistance to Bayer 205. This artificially produced resistance differs from the natural resistance of *T. rhodesiense*, since it survives prolonged passage through mice and tsetse flies.

These facts represent a real danger in Africa, where these drugs are being injected into whole populations of people without proper precautions to ensure that the treatment is always continued until it is effective. It is probable that a strain of trypanosomes is being developed which will resist treatment. Later in the discussion, however, Dr. C. M. Wenyon gave reasons for believing that this development of immunity is due to the selection of resistant trypanosomes.

Sir Henry Dale, in opening the general discussion, expressed the belief that quantitative studies can only give superficial information. He agreed with Prof. Straub that the most important problem is the explanation of the fact that certain drugs affect certain tissues in very low concentrations and have no action on other tissues.

Among those who made impromptu contributions was Dr. F. Hawking, who discussed the effect of chemical structure on the action of organic arsenicals consisting of a benzene ring, a side chain containing arsenic, and a second side chain. The absorption of such substances by trypanosomes can be demonstrated. Trypanosomes which are resistant to treatment *in vivo*, fail to absorb substances containing the second side chain. Similar substances containing no second side chain are taken up, even by undamaged resistant trypanosomes.

Sir Rickard Christophers, discussing the chemical structure of antimalarial drugs, pointed out that it is difficult to predict the action of new substances. This is perhaps because insufficient attention is given to the physicochemical properties of these substances.

Preliminary measurements of solubilities and of *p*K's might discriminate between substances worth testing and those which would be useless.

Prof. R. Robinson asked why it is that plants so often contain alkaloids with marked actions on animal tissues. This may be explained by some theory of the biological history of the animals and plants which have developed together, or it may be due to the fact that the alkaloids are probably degradation products of proteins, since their structure can usually be derived formally from the naturally occurring amino acids.

Magnetic Properties of the Nickel-Iron Alloys

IN a pamphlet issued by the Bureau of Information on Nickel of the Mond Nickel Co., Ltd., Millbank, S.W.1, an account is given of nickel-iron alloys and their characteristics which will be of special value to electrical engineers and manufacturers.

The magnetic properties present very striking contrasts. The permeability of pure iron, for example, is gradually reduced by additions of nickel exceeding ten per cent, until in the region of 30 per cent the alloys are completely non-magnetic. Further additions of nickel give a range of alloys containing 35–85 per cent of nickel, which have a very high magnetic permeability and are in fact the softest materials magnetically that are commercially available. New alloys have now been developed by adding substantial proportions of nickel and aluminium, which are very hard and form permanent magnets of great strength. The 25 per cent nickel steel is characterized by an extremely high ductility and is corrosion resisting. It is practically non-magnetic and is used extensively in electrical engineering.

The group of iron alloys having 35–80 per cent of nickel, on account of their high permeability, are of great commercial importance. In 1921 the Western Electric Co. of America took out a patent for an alloy consisting of 78·5 per cent nickel and 21·5 per cent iron, all impurities being kept as low as possible. The heat treatment necessary consisted in heating the alloy to 900° C. and then cooling at a definite rate. The alloys patented by this company are given the general name of 'permalloy'. Since then, patents have been taken out for other nickel-iron alloys, containing small proportions of other elements. 'Mumetal', patented by the Telegraph Construction and Maintenance Co., Ltd., London, is one of these. It contains 6 per cent of copper, which facilitates heat treatment and stabilizes the alloy.

The first use to which the high permeability alloys were put was for the 'loading' of submarine cables. In accordance with Heaviside's theory, this would prevent distortion of the signals and also their attenuation. Simultaneously with the development of the loaded submarine cable, continuous attention was given to long-distance land line cables, and nickel-iron devices were found very helpful. Afterwards, in order to save space, it was found advantageous to employ the magnetic alloy in the form of dust or powder. Various chemical and physical methods are used to produce the alloy in this form. A drawback is that the powder has very low permeability, but the energy losses in it are much smaller.

In the year 1930, news first came from Japan of the discovery of a new series of permanent magnet alloys in which the principal alloying elements were nickel and aluminium. Since their introduction, these new magnet steels have been intensively studied, and they are now superseding the cobalt and other steels previously used for these applications. These alloys offer the maximum magnetic energy per unit volume yet available to manufacturers. One of the most important applications of the new magnets is for radio loud speakers. In the manufacture of small motors, magnetos and other small-sized dynamo electric equipment, the nickel alloy magnets are found very efficient and adaptable. They are used in the magnetic detectors used in 'automatic' traffic signalling.

On the theoretical side, our knowledge of magnetic alloys is far from complete. When we have a better knowledge of how heat treatment affects them, still more useful alloys may become available.

Educational Topics and Events

CAMBRIDGE.—The Vice-Chancellor has received a letter from Sir Harry McGowan, chairman of Imperial Chemical Industries, Ltd., stating that it is not proposed to continue to support financially the work on molecular rays carried out since 1929 by Mr. R. G. J. Fraser, who has now been appointed to the research staff of I.C.I. (Alkali) Ltd. The apparatus and equipment installed, at a cost of about £2,500, is being offered to the University for the use of the Departments of Chemistry and Physics, and Sir Harry hopes that it will continue to be used for research on molecular rays.

The Managers of the Benn W. Levy Fund have appointed K. P. Harrison, of King's College, to the studentship in biochemistry.

J. H. Gaddum (Trinity College), W. B. R. King (Magdalene College) and Dr. O. M. B. Bulman (Sidney Sussex College) have been approved for the degree of Sc.D.

The Governing Body of Emmanuel College invites applications for a research studentship which will be awarded in July 1937. Preference will be given to candidates who have already completed one but not more than two years of research. The studentship, which must be held at Emmanuel College, and has a maximum annual value of £150, is awarded and normally held for two years, but may be renewed for a third. Further information can be obtained from the Master of the College.

LONDON.—The title of professor of pathology of mental disease in the University has been conferred on F. L. Golla, in respect of the post held by him at the Maudsley Hospital; that of professor of psychiatry in the University on Dr. Edward Mapother, in respect of the post held by him at the Maudsley Hospital, and that of reader in mathematics in the University on Dr. L. S. Bosanquet, in respect of the post held by him at University College.

The following doctorates have been conferred: D.Sc. in botany on H. Chaudhuri (Imperial College—Royal College of Science); D.Sc. in horticulture on R. G. Hatton (East Malling Research Station); D.Sc. in physics on F. C. Chalklin (King's College).